INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/11529

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 7/42, 7/025, A01N 25/34, 31/04
US CL : 424/59, 64, 402;514/725, 937, 946

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/59, 64, 402;514/725, 937, 946

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

NONE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,536,740 A (GRANGER et al) 16 July 1996, see entire document.	1-19

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 16 JUNE 2000	Date of mailing of the international search report 25 JUL 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer SHARON HOWARD Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet) (July 1998)*

PA JT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing: 09 November 2000 (09.11.00)	
International application No.: PCT/US00/11529	Applicant's or agent's file reference: 550.0122WOQ
International filing date: 28 April 2000 (28.04.00)	Priority date: 29 April 1999 (29.04.99)
Applicant: MARTIN, Dennis, M. et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International preliminary Examining Authority on:

21 August 2000 (21.08.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer:

J. Zahra

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: CHARLES N.J. RUGGIERO
OHLANDT, GREELEY, RUGGIERO & PERLE, L.L.P.
ONE LANDMARK SQUARE, 9TH FLOOR
STAMFORD, CT 06901-2682

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of Mailing *(day/month/year)*	18 APR 2001
Applicant's or agent's file reference: 550.0122WOQ	REPLY DUE within TWO months from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/11529	28 APRIL 2000	29 APRIL 1999

International Patent Classification (IPC) or both national classification and IPC
IPC(7): A61K 7/42, 7/025, A01N 25/34, 31/04 and US Cl.: 424/59, 64, 402;514/725, 937, 946

Applicant
AVON PRODUCTS, INC.

1. This written opinion is the first (first, etc.) drawn by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I [X] Basis of the opinion
- II [ ] Priority
- III [ ] Non-establishment of opinion with regard to novelty, inventive step or industrial applicability
- IV [ ] Lack of unity of invention
- V [X] Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI [ ] Certain documents cited
- VII [ ] Certain defects in the international application
- VIII [ ] Certain observations on the international application

RECEIVED
OHLANDT, GREELEY
RUGGIERO & PERLE

3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. ~~The applicant may, before the expiration of that time limit, request this Authority to grant an extension., see Rule 66.2(d).~~

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 *bis*.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 29 AUGUST 2001.

Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer SHARON HOWARD
Facsimile No. (703) 305-3230	Telephone No. (703) 308-1235

Form PCT/IPEA/408 (cover sheet) (July 1998)*

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: CHARLES N.J. RUGGIERO
OHLANDT, GREELEY, RUGGIERO & PERLE, L.L.P.
ONE LANDMARK SQUARE, 9TH FLOOR
STAMFORD, CT 06901-2682

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of Mailing *(day/month/year)*	18 APR 2001
Applicant's or agent's file reference 550.0122WOQ	REPLY DUE within TWO months from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/11529	28 APRIL 2000	29 APRIL 1999

International Patent Classification (IPC) or both national classification and IPC
IPC(7): A61K 7/42, 7/025, A01N 25/34, 31/04 and US Cl.: 424/59, 64, 402;514/725, 937, 946

Applicant
AVON PRODUCTS, INC.

1. This written opinion is the first (first, etc.) drawn by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I [X] Basis of the opinion
- II [ ] Priority
- III [ ] Non-establishment of opinion with regard to novelty, inventive step or industrial applicability
- IV [ ] Lack of unity of invention
- V [X] Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI [ ] Certain documents cited
- VII [ ] Certain defects in the international application
- VIII [ ] Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. ~~The applicant may, before the expiration of that time limit, request this Authority to grant an extension., see Rule 66.2(d).~~

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 *bis*.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 29 AUGUST 2001.

Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer SHARON HOWARD Telephone No. (703) 308-1235

Form PCT/IPEA/408 (cover sheet) (July 1998)*

WRITTEN OPINION

International application No.
PCT/US00/11529

I. Basis of the opinion

1. With regard to the elements of the international application:*

[X] the international application as originally filed

[X] the description:
pages 1-20, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of ____

[X] the claims:
pages 21-24, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of ____

[X] the drawings:
pages 1-6, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of ____

[X] the sequence listing part of the description:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of ____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language ____ which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

[ ] contained in the international application in printed form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the writen sequence listing has been furnished.

4. [X] The amendments have resulted in the cancellation of:

[X] the description, pages NONE

[X] the claims, Nos. NONE

[X] the drawings, sheets/~~fig~~ NONE

5. [ ] This opinion has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*

WRITTEN OPINION

International application No.
PCT/US00/11529

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	1-19	YES
	Claims	NONE	NO
Inventive Step (IS)	Claims	NONE	YES
	Claims	1-19	NO
Industrial Applicability (IA)	Claims	1-19	YES
	Claims	NONE	NO

2. citations and explanations

Claims 1-19 lack an inventive step under PCT Article 33(3) as being obvious over Bissett (U.S. 6,051,602) in view of Wilmott et al. (4,826,828).

Bissett teaches methods for regulating the appearance of fine lines, wrinkes and aging skin, by applying a safe and effective amount of a composition (col.7, lines 45-52) comprising 0.75-1.50% of retinol (col.11, Example 4), to the lips (col.8, lines 26-27). Bissett discloses that the composition is in the form of a gel, an emulsion, spray or a lipstick which defines a cosmetically acceptable vehicle (col.8, lines 17-21) and the composition further comprises a sunscreen (i.e. titanium dioxide)(col.7, line 1).

Bissett also discloses an emulsion vehicle, as well as anhydrous vehicles (oils, alcohol and silicones)(col.6, lines 10-20).

Bissett differs from applicant's claimed invention by not specifically teaching that the composition comprises a penetration enhancing agent.

However, Wilmott teaches a composition and method for reducing wrinkes, comprising using a stable amount (0.005 to 1.0 weight percent) of retinol and ethanol (i.e. a penetration enhancer) which is known in the art for reducing wrinkes and fine lines with minimal irritation of the skin (col.1, lines 61-66). The composition also comprises sunscreen which included benzophenone-3 and octyl dimethyl PABA.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the teachings of a penetration enhancing agent taught by Wilmott in the teachings of Bissett with the expected benefit of achieving a composition which is known in the art to treating the condition of the skin or lips.

Claims 1-19 meet the criteria of PCT Artile 33(4) because the composition is useful as a lip cream.

---------- NEW CITATIONS ----------

US 6,051,602 A (DONALD BISSETT) 18 April 2000, col.6, lines 18-(Continued on Supplemental Sheet.)

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

TIME LIMIT:

The time limit set for response to a Written Opinion may not be extended. 37 CFR 1.484(d). Any response received after the expiration of the time limit set in the Written Opinion will not be considered in preparing the International Preliminary Examination Report.

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):
20, col.6, lines 58-67, col.7, lines 1-5, col.8, lines 17-28.

US 4,826,828 A (WILMOTT et al) 02 May 1989, col.1, lines 61-66, col. 2, lines 19-54.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: CHARLES N.J. RUGGIERO
OHLANDT, GREELEY, RUGGIERO & PERLE, L.L.P.
ONE LANDMARK SQUARE, 9TH FLOOR
STAMFORD, CT 06901-2682

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

Date of Mailing *(day/month/year)* 25 JUL 2000	
Applicant's or agent's file reference 550.0122WOQ	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US00/11529	International filing date *(day/month/year)* 28 APRIL 2000
Applicant AVON PRODUCTS, INC.	

1. [X] The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the international search report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in rules 90 *bis* 1 and 90 *bis* 3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer SHARON HOWARD Dorothea Lawrence for
Facsimile No. (703) 305-3230	Telephone No. (703) 308-1235

(See notes on accompanying sheet)

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: CHARLES N.J. RUGGIERO
OHLANDT, GREELEY, RUGGIERO & PERLE, L.L.P.
ONE LANDMARK SQUARE, 9TH FLOOR
STAMFORD, CT 06901-2682

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JUL 28 2000
OHLANDT, GREELEY, RUGGIERO & PERLE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference 550.0122WOQ	Date of Mailing *(day/month/year)* 25 JUL 2000 **FOR FURTHER ACTION** **See paragraphs 1 and 4 below**
International application No. PCT/US00/11529	International filing date *(day/month/year)* 28 APRIL 2000
Applicant AVON PRODUCTS, INC.	

1. [X] The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the international search report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in rules 90 *bis* 1 and 90 *bis* 3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer SHARON HOWARD Telephone No. (703) 308-1235

Form PCT/ISA/220 (July 1998)★ *(See notes on accompanying sheet)*

TENT COOPERATION TREA

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 550.0122WOQ	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/US00/11529	International filing date *(day/month/year)* 28 APRIL 2000	(Earliest) Priority Date *(day/month/year)* 29 APRIL 1999
Applicant AVON PRODUCTS, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 2 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (See Box II).

4. With regard to the **title**,

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 5

[X] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

[ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/11529

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 7/42, 7/025, A01N 25/34, 31/04
US CL : 424/59, 64, 402;514/725, 937, 946

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/59, 64, 402;514/725, 937, 946

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

NONE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,536,740 A (GRANGER et al) 16 July 1996, see entire document.	1-19

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 16 JUNE 2000	Date of mailing of the international search report 25 JUL 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer SHARON HOWARD Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet) (July 1998)★

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under Article 19. The Notes are based on the requirements of the Patent Cooperation Treaty and of the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule" and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended ?

The claims only.

The description and the drawings may only be amended during international preliminary examination under Chapter II.

When ? **Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).**

Where not to file the amendments ?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How ? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

What documents must/may accompany the amendments ?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confounded with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

(i) the claim is unchanged;
(ii) the claim is cancelled;
(iii) the claim is new;
(iv) the claim replaces one or more claims as filed;
(v) the claim is the result of the division of a claim as filed.

PCT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: CHARLES N.J. RUGGIERO
OHLANDT, GREELEY, RUGGIERO & PERLE, L.L.P.
ONE LANDMARK SQUARE, 9TH FLOOR
STAMFORD, CT 06901-2682

PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing *(day/month/year)*	12 OCT 2001
Applicant's or agent's file reference 550.0122WOQ	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority Date *(day/month/year)*
PCT/US00/11529	28 APRIL 2000	29 APRIL 1999

Applicant
AVON PRODUCTS, INC.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

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Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	SHARON HOWARD
Facsimile No. (703) 305-3230	Telephone No. (703) 308-1234

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 550.0122WOQ	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US00/11529	International filing date *(day/month/year)* 28 APRIL 2000	Priority date *(day/month/year)* 29 APRIL 1999
International Patent Classification (IPC) or national classification and IPC IPC(7): A61K 7/42, 7/025, A01N 25/34, 31/04 and US Cl.: 424/59, 64, 402;514/725, 937, 946		
Applicant AVON PRODUCTS, INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

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   II ☐ Priority

   III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability

   IV ☐ Lack of unity of invention

   V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

   VI ☐ Certain documents cited

   VII ☐ Certain defects in the international application

   VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
21 AUGUST 2000	16 AUGUST 2001
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer SHARON HOWARD Telephone No. (703) 308-1235

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US00/11529

I. Basis of the report

1. With regard to the **elements** of the international application:*

[X] the international application as originally filed

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pages 1-20, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

[X] the claims:
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pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

[X] the drawings:
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pages NONE, filed with the demand
pages NONE, filed with the letter of _____

[X] the sequence listing part of the description:
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pages NONE, filed with the demand
pages NONE, filed with the letter of _____

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[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

[ ] contained in the international application in printed form.

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[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

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4. [X] The amendments have resulted in the cancellation of:

[X] the description, pages NONE

[X] the claims, Nos. NONE

[X] the drawings, sheets/~~fig~~ NONE

5. [X] This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

***Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	1-19	YES
	Claims	NONE	NO
Inventive Step (IS)	Claims	1-19	YES
	Claims	NONE	NO
Industrial Applicability (IA)	Claims	1-19	YES
	Claims	NONE	NO

2. citations and explanations (Rule 70.7)

Claims 1-19 meet the criteria set out in PCT Article 33(2)-(4), because neither cited patent teaches the application of their respective compositions to the epithelia, i.e. the lips., let alone improving the aesthetic appearance of the epithelia.

The composition is useful as a lip cream.

---------- NEW CITATIONS ----------

US 6,051,602 A (DONALD BISSETT) 18 April 2000, col. 6, lines 18-20, col. 6, lines 58-67, col. 7, lines 1-5, col. 8, lines 17-28.

US 4,826,828 A (WILMOTT et al) 02 May 1989, col. 1, lines 61-66, col. 2, lines 19-54.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

I. BASIS OF REPORT:

5. (Some) amendments are considered to go beyond the disclosure as filed:
NONE

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

REC'D 16 OCT 2001
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(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 550.0122WOQ	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
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Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer SHARON HOWARD Telephone No. (703) 308-1235

Form PCT/IPEA/409 (cover sheet) (July 1998) ★

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International Application No.
PCT/US00/11529

I. Basis of the report

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[X] the claims:
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INTERNATIONAL PRELIMINARY [redacted]MINATION REPORT

International application No.
PCT/US00/[redacted]

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	1-19	YES
	Claims	NONE	NO
Inventive Step (IS)	Claims	1-19	YES
	Claims	NONE	NO
Industrial Applicability (IA)	Claims	1-19	YES
	Claims	NONE	NO

2. citations and explanations (Rule 70.7)

Claims 1-19 meet the criteria set out in PCT Article 33(2)-(4), because neither cited patent teaches the application of their respective compositions to the epithelia, i.e. the lips., let alone improving the aesthetic appearance of the epithelia.

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Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

I. BASIS OF REPORT:

5. (Some) amendments are considered to go beyond the disclosure as filed:
NONE

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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09/301,570 29 April 1999 (29.04.99) US

(71) Applicant *(for all designated States except US)*: AVON PRODUCTS, INC. [US/US]; 1251 Avenue of the Americas, New York, NY 10020–1196 (US).

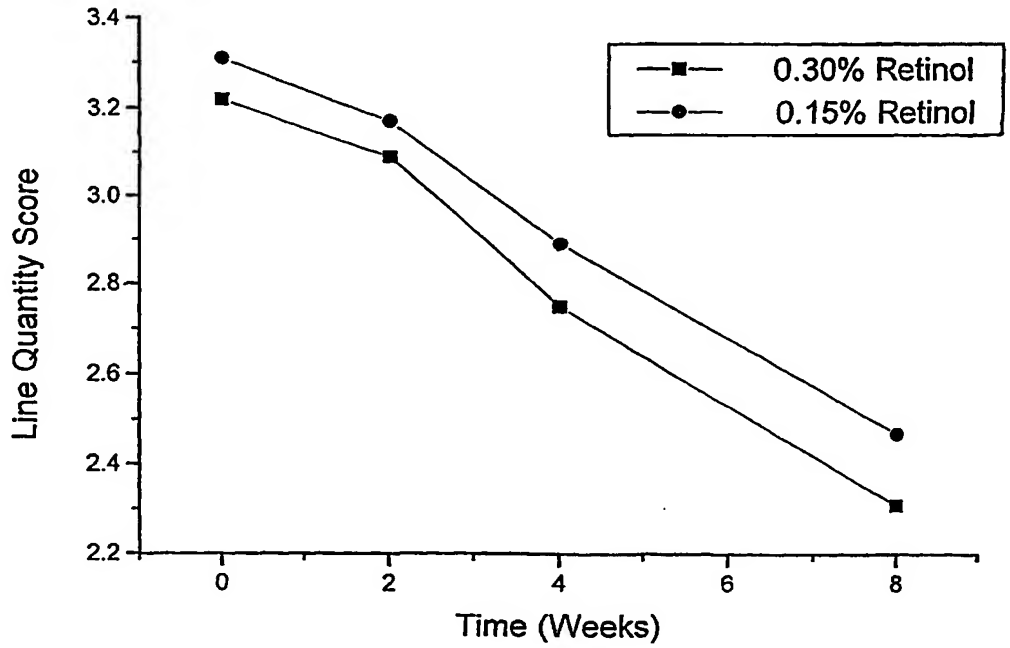
(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: MARTIN, Dennis, M. [US/US]; 8 Tenney Lane, Cornwall, NY 12518 (US). TRAUDT, Michael [US/US]; 17 Mountainview Drive, Brookfield, CT 06804 (US). ATTAR, Paul [US/US]; 23 Metro Vista Drive, Hawthorne, NJ 07506 (US). MORELLI–ABRAMS, Isabella [US/US]; 516 Willow Grove Road, Stony Point, NY 10980 (US).

(74) Agent: RUGGIERO, Charles, N., J.; Ohlandt, Greeley, Ruggiero & Perle, LLP, One Landmark Square, 9th Floor, Stamford, CT 06901–2682 (US).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: METHOD OF IMPROVING THE AESTHETIC APPEARANCE OF EPITHELIA



(57) Abstract

An effective treatment method for improving the appearance of epithelia, such as lip epithelia and vaginal epithelia is provided. According to the present method, an effective amount of a composition containing retinoid, preferably in a cosmetically acceptable carrier, is topically applied to the vaginal or lip epithelia. The present invention also includes compositions for practicing the method.

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METHOD OF IMPROVING THE AESTHETIC APPEARANCE OF EPITHELIA

BACKGROUND OF THE INVENTION

This application claims priority in U.S. Patent Application Ser. No. 09/301,570, filed April 29, 1999.

1. Field Of The Invention

The present invention relates to a method of improving or re-moisturizing the epithelia. More particularly, the present invention relates to a method of improving lip color and reducing the number and depth of lip lines on the surface of the lips, as well as re-moisturizing the vagina and lips. This is achieved by using a composition comprising a retinoid, such as retinol, and a penetration enhancing agent in a cosmetically acceptable carrier. The present invention also relates to a composition, which comprises a retinoid, and to a process for preparing the composition.

2. Description Of The Prior Art

Retinol is known for its beneficial effects in the treatment of acne. In the field of repair of damage caused either by age or overexposure to the sun, retinol has been proven beneficial. Repeated application of cosmetic compositions containing retinol has been used to smooth the skin surface, repair small cracks in the epidermis and to remove wrinkles or minimize the formation thereof.

Because the anatomy and physiology of vagina and the lips differ greatly from the anatomy and physiology of skin proper, the use of retinol for re-moisturizing, treating a color deficiency and/or treating vertical lines, does not have an obvious correlation to skin aging pathologies. As known in the art, vertical lip lines are visually distinguishable from general wrinkling of the lips. As the term "vertical" implies, vertical lip lines appear as substantially vertical creases, whereas "wrinkling" has no such discernible form.

However, it is well known that orally administered retinoids, such as, for example, retinol and retinoic acid, dry out the epithelia and cause cornification of mucosal epithelia.

Research on beneficial effects of retinol has been directed to cosmetic "skin" to produce a reduction in wrinkles and other skin effects related to or resulting from aging. However, there are no reports relating to a method of re-moisturizing the epithelia, improving lip color or reducing the number and depth of lip lines, particularly vertical lip lines, using retinol. Moreover, there are no reports of reversing age-associated cornification of the vaginal or lip epithelia.

Surprisingly, it has been discovered that topically applying a composition including retinoid, such as retinol, and a penetration enhancing agent to mucosal or semi-mucosal epithelium that is dried out and/or cornified, re-moisturizes the epithelium. Furthermore, with repeated application, the cornified epithelia returns to its original mucosal state.

Related U.S. Patent Nos. 5,656,672 and 5,800,596 provide a water-in-oil emulsion cream, containing retinol, for use as a nourishing and repairing care product for damaged and wrinkled lips.

U.S. Patent No. 4,826,828 is directed to a water-in-oil emulsion containing retinol, a volatile silicone and a solvent for both the retinol and the volatile silicones. This patent also provides preparation of a retinol emulsion by adding a solution containing retinol to a water-in-oil emulsion. However, to avoid degradation, the retinol is added to the emulsion just prior to or at the time of use. It is apparent that the stability of retinol in a composition of this type is insufficient for prolonged storage prior to use.

U.S. Patent No. 5,124,313 provides topical compositions having a retinyl ester-polypeptide complex, specifically a retinyl palmitate-polypeptide complex.

WO 93/00085 provides stabilization of retinol in cosmetic compositions by addition to the latter a stabilizing complex comprising, in combination, an antioxidant and a chelating agent for chelating metal ions. The stability of the retinol appears enhanced due to considerable amounts of stabilizing antioxidants and chelating agents in the composition.

WO 97/02814 provides the preparation of an antibacterial medicament containing a retinoid for rapid bactericidal action, particularly on Gram positive bacteria, which accelerates the repair of small lesions.

WO 97/02030 provides cosmetic, antimycotic compositions containing a glycol or glyceryl ester of retinoic acid. These compositions are used to produce visible reduction in wrinkles and visible improvement in tone, firmness and luminosity of skin.

Thus, there as been a need for a topical retinol composition that provides a method for restoring the aged, cornified vaginal epithelia and cornified human lips to their original mucosal state.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide a method of re-moisturizing epithelia, comprising topically applying to vaginal or lip epithelia an effective amount of a composition comprising a retinoid. The composition can further comprise a cosmetically acceptable carrier.

It is another object of the present invention to provide such a method of re-moisturizing vaginal and lip epithelia in older women,

improving lip color, lip clarity and lip dryness, and reducing the number and depth of lip lines.

It is yet another object of the present invention to provide a composition that can be used to re-moisturize vaginal and lip epithelia in older women and improve lip color, lip clarity and lip dryness, and reducing the number and depth lip lines.

These and other objects of the present invention will become apparent in the course of the following description of the preferred embodiments.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a plot of the average scores for dryness of lips;

Figure 2 is a plot of the average scores for dry appearance of lips;

Figure 3 is a plot of the average scores for clarity of lips;

Figure 4 is a plot of the average scores for color of lips;

Figure 5 is a plot of the average scores for line quantity of lips; and

Figure 6 is a plot of the average scores for line depth of lips.

DETAILED DESCRIPTION OF THE INVENTION

The anatomy and physiology of vagina and the lips of one's mouth differ in many ways from "skin" proper. Because of such differences, the use of a composition having a retinoid, such as retinol, for treating vaginal and lip dryness or treating color deficiency and/or lines of the lip is not an obvious correlation to the treatment of aging pathologies associated with

other types of skin. Thus, the present invention is the first to demonstrate a clinical benefit when applied topically to a vaginal epithelium and to a semi-mucosal epithelium, which is within and up to the vermilion border of the lips. In addition, the present invention is the first to demonstrate that the aesthetic appearance of epithelia is improved by applying a topical composition having both a retinoid, particularly retinol, in an amount effective to improve the aesthetic appearance of the epithelial and a penetration enhancing agent in an amount effective to enhance penetration of the retinoid into the epithelia. The applicants have unexpectedly discovered an effective method for improving human lip color (i.e., increasing redness) and reducing the number and depth of lip lines (i.e., line quantity), as well as re-moisturizing vaginal and lip epithelia in older women. As used in the context of the present invention, the term "older" refers to post-menopausal women and/or women who suffer from age-related vaginal and lip dryness or cornification.

When used as a vaginal treatment for re-moisturizing vaginal epithelia, the method of the present invention must be applied almost exclusively to older women who are experiencing routine vaginal dryness. The composition is preferably applied daily to inner surfaces of the vagina, before bedtime.

Without being bound by any theory, it is believed that, as they age, epithelial cells may lose responsiveness to circulating retinoids, such as retinol, causing a fundamental change in the structure of the cells, i.e., squamous metaplasia. With a supply of excess retinoid available to the cells, the cells respond and return to their mucosal state. The penetration enhancing agent provides improved delivery of the retinoid to the "active" site located at the epithelial cell.

A beneficial re-moisturizing effect is obtained on repeated application of the composition to the vaginal epithelia. To produce the

beneficial re-moisturizing effect of the method of the present invention, the composition is preferably applied to the vaginal epithelia in the form of a cream.

On repeated application of the composition to the lips, particularly aging lips, in accordance with the method of the present invention, a visible improvement in lip condition, moisturization, color, clarity and a measurable reduction in the number and depth of lip lines is observed within a short period of time, which can be as little as two (2) weeks, when applied once or twice a day. The improvement in the color of the lips is manifested by an increase in the redness of the lips, whereas the reduction in the number of lines is directly measured and reduction in the dryness and depth of the lines estimated by direct observation as described below.

In the context of the present invention, the term retinoid includes the following classes of compounds: retinol; esters of retinol with carboxylic acids of 1 to 24 carbon atoms, such as retinyl acetate, retinyl propionate, retinyl butyrate, retinyl octanoate, retinyl laurate, retinyl palmitate, retinyl oleate, retinyl linoleate; esters of retinol with alpha-hydroxy carboxylic acids; ether derivatives of retinol, including alkyl ethers, ethers derived from glycolic acid and glycolate esters and amides, such as retinyl glycolyl ether (retinyl glycolic acid ether); retinaldehyde; retinoic acid; esters of retinoic acid with alcohols of 1 to 24 carbon atoms; isotretinoin as well as synthetic retinoid mimics, and derivatives of the foregoing, as well as others that bind to RAR receptors; cis- and trans-isomers thereof; salts thereof; and mixtures thereof. Preferably, the retinoid is retinol. More preferably, the retinoid is the trans-isomer of retinol. Retinol may be prepared by well-known methods such as those described in U.S. Patent No. 3,060,229, the content of which is incorporated herein by reference.

Retinyl esters, which generally are less potent than other retinoids, are less preferred retinoids for the purposes of the present invention.

Specifically, retinyl ester-polypeptide complexes, such as those described in U.S. Patent No. 5,124,313, are not contemplated as retinoids within the context of the present invention.

The amount of retinoid in the composition of the present invention is preferably in the range from about 0.001 to about 1.5 weight percent (wt%) of the total composition, more preferably from about 0.06 wt% to about 0.3 wt%, and most preferably about 0.1 wt% to about 0.2 wt% of the composition. However, as stated above, the amount of retinoid may be adjusted, based upon the potency of the retinoid, without departing from the present invention.

The penetration enhancing agent is present in an amount effective to either enhance the penetration of the selected retinoid into the epithelia or increase the rate (i.e., speed) of penetration of the selected retinoid into the epithelia. Preferably, the penetration enhancing agent does both. The selection of the penetration enhancing agent will depend on formulation factors, such as the chemical properties of the selected retinoid and the vehicle (e.g., solution, emulsion, stick). Non-limiting examples of such penetration enchancing agents include: organic solvents, such as ethanol, glycols (e.g., propylene, butylene, pentylene), pyrrolidones (e.g., 2-pyrrolidone, 1-methyl-2-pyrrolidone, 5-methyl-2-pyrrolidone, 1,5-dimethyl-2-pyrrolidone, 1-ethyl-2-pyrrolidone, 2-pyrrolidone carboxylic acid), dimethyl sulfoxide, dimethylacetamide, and dimethylformadide); alkyl sulfoxide; phosphine oxide; sugar esters (e.g., sucrose acetate, sucrose octanoate); anionic surfactants; nonionic surfactants; Azone™ (e.g., 1-dodecylazaclo-heptan-2-one); N-substituted di-isopropanolamines; fatty acids (e.g., oleic acid, linoleic acid); and mixtures thereof. Additional resources are available to those in the art to assist with the selection of the penetration enhancing agent. One such resource is available at pages 160 through 172 of Dermatological Formulations, B.W. Barry (Marcel Decker, 1983), which is incorporated herein by reference.

In addition to the retinoid and the penetration enhancing agent, the composition of the invention can contain a cosmetically acceptable carrier. The carrier can be water, a humectant, a thickener, a gelling agent, an oil, an emulsifier, or mixtures thereof. The resulting composition can be in the form of a cream, dispersion, emulsion, foam, gel, solution, stick suspension, spray, patch, powder or in a towelette. The emulsion can be either an oil-in-water emulsion or a water-in-oil emulsion.

Preferably, the retinoid is formulated into an appropriate vehicle consistent with consumer requirements. For example, the composition can preferably be formulated as a stick or cream for treatment of the lips. For the treatment of the vaginal epithelia, the composition would preferably be formulated as a cream.

The oil phase of the emulsion preferably has one or more organic compounds, including emollients. The aqueous phase has humectants, such as propylene glycol and glycerin; other water-dispersible or water-soluble components including thickeners such as veegum or hydroxyalkyl cellulose; gelling agents, such as high MW polyacrylic acid, i.e. carbopol 934; and mixtures thereof. The emulsion has one or more emulsifiers capable of emulsifying the various components present in the composition, including the retinoids. Because of the light, heat and air sensitivity of retinoids, retinoids are generally added last in the preformed emulsion so as to minimize exposure to light, heat and oxygen.

Non-limiting examples of organic compounds suitable for use in the oil phase include emollients, skin conditioning agents, solvents that are capable of dissolving retinol or retinoids without reducing the stability thereof, and mixtures thereof. The compounds suitable for use in the oil phase include one or more of the following: an alcohol including cetyl alcohol; ester including cetyl recinoleate, sterol esters; carboxylic acid; mineral oil; wax; hydrocarbon; paraffin; isoparaffin; petrolatum; low taste

petrolatum for application on lips; hydrogenated polydecene; silicone-containing compound such as dimethyl polysiloxane; and mixtures thereof.

The emulsifier can be an emulsifying wax, an emulsifying polyhydric alcohol, a polyether polyol, a polyether, a mono- or di-ester of a polyol, an ethylene glycol mono-stearate, a glycerin mono-stearate, glycerin di-stearate, a silicone-containing emulsifier, a soya sterol, a fatty alcohol such as cetyl alcohol, a fatty acid such as stearic acid, a fatty acid salt, and mixtures thereof. The preferred emulsifiers include soya sterol, cetyl alcohol, stearic acid, emulsifying wax, and mixtures thereof.

The emulsifying waxes that are suitable for use in the present invention are well known to persons skilled in the art. The emulsifying wax includes compositions such as those containing about 80 wt% cetearyl alcohol, about 10 wt% polysorbate 60, about 5 wt% stearate, and about 5 wt% steareth-20.

In the emulsion, the aqueous phase is preferably from about 60 wt% to about 90 wt%, the oil phase is preferably from about 5 wt% to about 30 wt% of the emulsion, and the emulsifier is preferably from about 5% to about 10 wt% of the emulsion.

The emulsion according to the present invention has pH preferably in the range from about 6.5 to about 7.5.

The composition according to the present invention can be prepared by dissolving a retinoid, such as retinol, in a medium comprising an organic solvent, and optionally water, and adding the resulting homogeneous solution to the emulsion. The composition produced thereby preferably has from about 0.001 wt% to about 1.0 wt% retinol, on an active basis, and about 0.5 wt% to about 1.0 wt% organic solvent. More preferably, the composition has from about 0.06 wt% to about 0.3 wt% retinol.

The present invention includes a process for preparing a composition comprising a retinoid, such as retinol, in the form of a cream, dispersion, emulsion, foam, gel, solution, stick or suspension.

The process for preparing a composition for re-moisturizing epithelia, comprises:

preparing a first mixture comprising water, a humectant, a thickener, and a gelling agent;

preparing a second mixture comprising an oil and an emulsifier;

adding the second mixture and the first mixture together, preferably mixing the second mixture in the first mixture, at a temperature and period of time sufficient to produce a stable emulsion;

cooling the stable emulsion; and

adding a retinoid to the stable emulsion to produce the composition.

In addition, the present invention may include a secondary component. The secondary component is preferably selected from one or more of the following thirteen groups.

1. Rexinoids: Rexinoids include compounds, such as all-trans retinoic acid, 9-cis retinoic acid, phytanic acid and others, that bind to RXR receptors.

2. An estrogen synthetase (aromatase) stimulating compound: Examples of such a compound include caffeine and/or derivatives thereof, and any mixture thereof. Caffeine is the more preferred of such compounds.

3. A compound capable of inhibiting 5 alpha-reductase activity: Examples of such a compound include linolenic acid, linoleic acid, finasteride, and mixtures thereof.

4. An exfoliation promoting compound: Suitable examples include alpha hydroxy acids; beta hydroxy acids; oxa acids as disclosed in U.S. Patent No. 5,847,003 (the disclosure of which is incorporated herein by reference); oxa diacids as disclosed in U.S. Patent No. 5,834,513 (the disclosure of which is incorporated herein by reference); mechanical exfoliation compounds, such as bamboo exfoliant extract; salicylic acid; benzoyl peroxide; keto acids, such as pyruvic acid, 2-oxopropanoic acid, 2-oxobutanoic acid, and 2-oxopentanoic acid; and mixtures thereof.

The preferred exfoliation promoting compounds are lactic acid, glycolic acid, 3,6,9-trioxaundecanedioic acid, and any mixture thereof. When the present invention includes an exfoliation promoting compound, the composition comprises about 1 wt% to 20 wt%, preferably about 1 wt% to about 15 wt%, more preferably about 4 wt% to about 10 wt% acid, and most preferably about 4 wt%, of the exfoliation promoting compound.

5. An ultraviolet (UV) light protecting/sunscreen agent: Examples include organic and inorganic sunscreens, such as titanium dioxide, zinc oxide, methyl benzylidene camphor and/or its derivatives, octocrylene, anthranilates, benzophenones, butylmethoxydibenzoylmethane (avobenzone), naphtholsulphonates, benzoic acid derivatives, salicylates, cinnamic acid derivatives, terephthalylidene dicamphor sulfonic acids, and mixtures thereof. Of these, butylmethoxydibenzoylmethane, octocrylene, octylsalicylate, octylmethoxycinnamate, oxybenzone, titanium dioxide, and mixtures thereof are preferred. Butylmethoxydibenzoylmethane, oxybenzone, octylmethoxycinnamate, terephthalylidene dicamphor sulfonic acids, and mixtures thereof are most preferred. Salts, esters and other derivatives of the aforementioned sunscreen agents, which are compatible with the composition, are also contemplated in practicing the present invention. A preferred UV absorber includes a hydroxybenzophenone

derivative, a benzotriazole derivative, a dibenzoyl methane derivative, an oxanilide derivative, a hydroxy cinnamate derivative, and mixtures thereof.

Co-formulation with an ultraviolet light protecting/sunscreen agent is particularly desirable when the present invention is used for treating lip epithelia, particularly for users who engage in activities, particularly outdoor activities, which expose the user's lip epithelia to UV radiation. Non-limiting examples of such activities include indoor tanning, sunbathing, and skiing. It is preferred that the sunscreen comprises from about 2 wt% to about 20 wt%, more preferably about 2 wt% to about 15 wt%, of the total weight of the composition.

6. Barrier function enhancing agents: Examples include ceramides; essential fatty acids and their esters, especially glycerides, α-hydroxy fatty acids and their esters, ω-hydroxy fatty acids and their esters; phospholipids; cholesterol and its esters, such as cholesteryl hemisuccinate, cholesteryl phosphate; and cholestanol and its derivatives. The barrier function enhancing agent can be added to a topical composition either as singular molecular entities or as a complex mixture of lipids derived from either synthetic, animal or plant sources.

7. Collagen enhancing agents: These agents prevent epithelia "sagging" by promoting a net increase in collagen, either by reducing collagen breakdown or by promoting collagen formation. Examples of such agents include Clara extract (Sophora augustifolia), ascorbyl-phoshoryl-cholesterol, ascorbic acid, ascorbic acid derivatives, and mixtures thereof.

8. Elastase inhibitors: Examples of these inhibitors include fatty acids, such as oleic acid, perinaric acid, and Honeysuckle extract (Lonicera caprifolium). These inhibitors act to prevent sagging of the epithelia.

9. Skin lightening agents: Examples include kojic acid, hydroquinone, licorice derivatives, ascorbic acid/ascorbic acid derivatives (e.g. magnesium ascorbyl phosphate), arbutin, bearberry (Arctostaphylos uva ursi), Glycyrrhiza glabra and its derivatives, Chlorella vulgaris extract, and mixtures thereof.

10. Antioxidants: Examples include compounds having phenolic hydroxy functions, such as ascorbic acid, ascorbic acid derivatives; gallic acid derivatives (e.g. propyl gallate); ferulic acid derivatives (e.g. ethyl ferulate, sodium ferulate); nitrones; N-tertbutyl-nitrone; I-(4-pyridyl-1-oxide)-N-tertbutyl-nitrone; curcumin, tetrahydrocurcumin; 6-hydroxy-2,5,7,tetramethylchroman-2-carboxylic acid; uric acid; reductic acid; tannic acid; rosmarinic acid; tocopherol and its derivatives; catechins; and mixtures thereof. Other suitable antioxidants are those that have one or more thiol functions (-SH), in either reduced or non-reduced form, such as glutathione, lipoic acid, thioglycolic acid, and other sulfhydryl compounds. The antioxidant may be inorganic, such as sulfites, bisulfites, metabisulfite, or other inorganic salts and acids containing sulfur. Preferably, the antioxidant is selected from the group consisting of: a phenolic antioxidant such as butylated hydroxytoluene; butylated hydroxyanisole; an alkyl paraben such as methyl, ethyl or propyl paraben; and any mixtures thereof.

11. Skin warming agents: Examples include vanillyl butylamid, capsaicin, and mixtures thereof.

12. Skin cooling compounds: Examples include menthol, menthyl glycerol, asymmetrical carbonates, thiocarbonates and urethanes, N-substituted carboxamides, ureas or phosphine oxides, menthyl lactate, menthone glycerine acetal, and any mixtures thereof.

13. Anti-pruretic/Anti-itch compounds: Non-limiting examples of such compounds include capsaicin, nonivamde, and corticosteroids. Co-formulation with an anti-pruretic/anti-itch compound may be desirable when the present invention is applied to itchy vaginal epithelia. A non-limiting example of when such co-formulation may be desirable includes when the user has a concurrent condition commonly referred to as a yeast (Candida albicans) infection.

The addition of the secondary component enhances the dermatological benefits achieved and the utilization for compositions of the present invention. The compositions of the present invention may include at least two secondary components, with each secondary component being selected from a different group.

The compositions of the present invention can include other cosmetic and pharmaceutical actives and excipients. Such suitable cosmetic and pharmaceutical agents include, but are not limited to, one or more of erythromycins, tetracyclines, salicylic acids, antifungals, vitamins, anti-inflammatory agents, antimicrobials, analgesics, nitric oxide synthase inhibitors, self-tanning agents, surfactants, moisturizers, stabilizers, preservatives, antiseptics, chelating agents, thickeners, emulsifiers, lubricants, humectants, chelating agents, skin penetration enhancers, skin cooling agents, emollients, fragrances, colorants, flavoring agents, pigments, and mixtures thereof.

Other conventional constituents including cosmetic and pharmaceutical additives may be added to the composition. These additives include: vitamins, such as tocopherol and ascorbic acid; vitamin derivatives such as ascorbyl monopalmitate; thickeners such as hydroxyalkyl cellulose; gelling agents; structuring agents such as bentonite, smectite, magnesium aluminum silicate and lithium magnesium silicate;

metal chelating agents such as EDTA; pigments such as zinc oxide and titanium dioxide; colorants; emollients; and humectants.

When the present invention is used to improve the aesthetic appearance of lip epithelia, the compositions of the present invention may be non-pigmented or pigmented. Lip compositions, such as lipsticks, often have pigments incorporated therein. An example of a pigment is iron oxides. However, when the composition is pigmented, it is preferred that the composition includes an ascorbyl-phosphoryl-cholesterol (APC) compound. Examples of suitable APC compounds are disclosed in WO 97/42960, which is commonly assigned and is incorporated herein by reference.

The addition of an APC compound in pigmented compositions of the present invention is particularly desirable when the pigment is an iron oxide. An example of such a pigmented composition may have from about 0.2 wt% to about 20 wt% of iron oxides in addition to the APC compound. One preferred example of such a topical composition has from about 5 wt% to about 7 wt% of iron oxides and about 1 wt% of the APC compound in a suitable vehicle. In the preferred example, the iron oxides are selected from the group consisting of iron oxide red 2259-preserved, iron oxides (yellow), iron oxides (black), and mixtures thereof. Additional advantages of including an APC compound are set forth in PCT WO 00/06091, which is commonly assigned and is incorporated herein by reference.

When the present invention is applied to lip epithelia, particularly in the form of a pigmented composition, it is preferred that the weight percentage of retinoid in the pigmented composition is adjusted to accommodate numerous re-application as may occur with topical lip compositions, such as lipsticks and lip balms.

Compositions of the present invention can be applied to epithelia for a period of time to improve the aesthetic appearance of the epithelia. The improvement in aesthetics can include at least one of the following:

a. reducing intrinsic aging;
b. reducing photoaging;
c. decreasing epithelial fragility;
d. preventing and reversing loss of collagen;
e. preventing epithelial atrophy;
f. promoting/accelerating cell turnover;
g. improving epithelial firmness/plumpness;
h. improving epithelial texture;
i. decreasing fine lines;
j. decreasing wrinkles;
k. improving epithelial tone;
l. enhancing epithelial thickness;
m increasing moisture retention;
n. minimizing epithelial discoloration; and
o. reversing age-associated cornification of epithelia.

Other improvements in the aesthetic appearance of epithelia are provided by the present invention. The above improvements are only examples of the improvements made possible by the present invention and are set forth for illustration only.

The Examples that follow are intended for illustrating the present invention and not for limiting the scope thereof.

Clinical Study Results

Efficacy of retinol-containing creams in reducing visible signs of aging lips was demonstrated as follows.

Two lip creams, Lip Cream A containing 0.15% active retinol and Lip Cream B containing 0.30% active retinol were prepared as shown below in TABLE 1.

TABLE 1
Preparation Of Lip Cream A And Lip Cream B

INGREDIENTS (Wt%)	LIP CREAM A	LIP CREAM B
Retinol Cream		
Retinol	0.30	0.15
Acrylates Copololymer	1.10	0.55
Carbopol/thickeners	0.90	0.90
Disodium EDTA	0.20	0.20
Glycerin	5.00	5.00
Propylene Glycol	0.56	0.56
Emollients	13.50	13.50
Emulsifiers	8.50	8.50
Preservatives	1.40	1.40
Anti-oxidants	0.10	0.10
Triethanolamine	1.00	1.00
Demineralized Water	qs	qs

The study was a double blind monadic design. A total of 36 female subjects who met the inclusion criteria ranging in age from 33 to 64 years were selected for this study. The subjects were in good general health, with no known allergies or sensitivities to lip products. The subjects had skin types I–III (predominantly I-II), were not pregnant or nursing, had full lips, exhibiting acceptable appearance of aging lips, including paleness, mild dryness and flaking of the surface, and some vertical lines, but not premature aging.

Each subject's lips were visually examined (baseline examination) and signs of dryness, flaking, paleness, fullness and lip lines were recorded.

The subjects were randomly divided into two groups and each group was asked to use one Lip Cream once a day, at night, shortly before bedtime, after cleansing their face prior to using the Lip Cream. They were asked to apply a small amount of product onto a finger and spread the product on both the upper and lower lip, avoiding the outer edges of the lips, with the lips closed, to avoid getting the product into the mouth. The use of usual lip products such as lipstick and/or lip balm was permitted except on examination days.

At baseline the following visual parameters were graded (5-point subjective scoring):

(1) Dryness (flaking): 0=no visible flakes, 5=severe flaking;
(2) Dry appearance (visible tightness): 0=none, 5=severe;
(3) Color: 0=very pale, 5=dark red;
(4) Clarity (transparency): 0=clear, 5=highly opaque;
(5) Number of lines: 0=none, 5=numerous; and
(6) Depth of lines: 0=shallow, 5=deep.

Lip Cream A and Lip Cream B were then dispensed and use instructions administered. Briefly, subjects were instructed to apply the test product to their lips once a day, before bedtime.

Subjects returned for follow-up visual grading after 2, 4 and 8 weeks. In addition, 35mm frontal lip photos were taken at baseline and after 8 weeks. Finally, a self-perception questionnaire was administered at 8-weeks.

TABLE 2 compares the average visual scores of the two treatment groups.

TABLE 2
Efficacy of Retinol-Containing Creams in Reducing Visible Signs of Aging Lips
Average Visual Scores

Feature Evaluated	Week	FORMULA A 0.3% Retinol Mean (N=18)	FORMULA B 0.15% Retinol Mean (N=18)
Dryness	0	1.00	1.06
	2	1.09	1.08
	4	0.44	0.56
	8	0.34	0.58
Dry Appearance	0	2.41	2.58
	2	2.44	2.53
	4	1.63	1.83
	8	1.09	1.36
Clarity	0	3.84	3.86
	2	3.53	3.58
	4	2.69	2.89
	8	1.91	2.00
Color	0	1.84	1.86
	2	2.06	2.06
	4	2.69	2.50
	8	3.09	2.83
Number of Lines	0	3.22	3.31
	2	3.09	3.17
	4	2.75	2.89
	8	2.31	2.47
Line Depth	0	1.84	2.03
	2	1.69	1.75
	4	1.50	1.67
	8	1.28	1.50

From the results obtained, it can be seen that:

(1) there was no statistical difference between the two treatment groups;

(2) both Lip Creams were clinically well tolerated without any adverse clinical response attributable to the use of Lip Cream A or Lip Cream B;

(3) all parameters improved after 8 weeks;

(4) most parameters improved at 4 weeks, except number of lines, dryness and the 0.15% retinol (Formula B) line depth score; and

(5) the percent improvement, calculated from the average scores within an interval, was always numerically superior for Lip Cream A containing 0.3% retinol than for Lip Cream B containing 0.15% retinol.

Calculation of percent improvement for Lip Cream A containing 0.3% retinol revealed a 68% improvement in lip color and 28% reduction in the number of vertical lip lines and 30% reduction in the depth of vertical lip lines within 8 weeks of treatment.

While the difference in efficacy between Lip Cream A and Lip Cream B was not large, the magnitude of improvements in dryness, dry appearance, color, clarity and lines of the lips obtained from Lip Cream A containing 0.3% retinol was greater for all measured parameters. In addition, both Lip Cream A and Lip Cream B were clinically well tolerated.

Figures 1 through 6 chart the average scores for each parameter. These graphs demonstrate that, for all parameters, the most dramatic improvement was observed between 2 and 4 weeks of Lip Cream use.

Features associated with aging lips, including dryness (flaking/taut), dry appearance, color, clarity and number and depth of lines were all significantly improved by the use of the retinol-containing Lip Cream A and Lip Cream B according to the present invention.

Obvious modifications and variations of the present invention are possible in light of the above teachings. It is therefore to be understood that such modifications not specifically described herein are within the scope of the appended claims. Also, singular used in the application can also mean plural of the same ingredient.

CLAIMS

WHEREFORE, IT IS CLAIMED:

1. A method of improving the aesthetic appearance of epithelia comprising:

applying to the epithelia a topical composition comprising:

a retinoid in an amount effective to improve the aesthetic appearance of the epithelia; and

a penetration enhancing agent in an amount effective to enhance penetration of said retinoid into the epithelia,

wherein said topical composition is applied to the epithelia for period of time effective to provide the improvement.

2. The method of claim 1, wherein the epithelia is selected from the group consisting of lip epithelia and vaginal epithelia.

3. The method of claim 2, wherein the epithelia is lip epithelia.

4. The method of claim 1, wherein the improvement in aesthetic appearance is a reduction in the appearance of aging of the lips.

5. The method of claim 4, wherein the aging of the lips is photoaging or intrinsic aging.

6. The method of claim 4, wherein the improvement in aesthetic appearance is selected from the group consisting of:

a. improvement in lip color;

b. improvement in lip dryness;

c. improvement in lip clarity;

d. reduction in the number vertical lip lines;

e. reduction in the depth of vertical lip lines;

f. improvement in lip dryness appearance; and

g. combinations thereof.

7. The method of claim 1, wherein said retinoid is in amount from about 0.001 wt% to about 1.5 wt% of the total weight of the composition.

8. The method of claim 1, wherein said retinoid is retinol.

9. The method of claim 1, wherein the penetration enhancing agent is selected from the group consisting of: an organic solvent, an alkyl sulfoxide, a phoshine oxide, a sugar ester, a anionic surfactant, a non-ionic surfactant; an Azone, a N-substituted di-isopropanolamine, a fatty acid alcohol, and mixtures thereof.

10. The method of claim 1, wherein the penetration enhancing agent is selected from the group consisting of ethanol, propylene glycol, butylene glycol, pentylene glycol, 2-pyrrolidone, 1-methyl-2-pyrrolidone, 5-methyl-2-pyrrolidone, 1,5-dimethyl-2-pyrrolidone, 1-ethyl-2-pyrrolidone, 2-pyrrolidone carboxylic acid, dimethyl sulfoxide, dimethylacetamide, dimethylformadide; alkyl sulfoxide; phosphine oxide; sucrose acetate, sucrose octanoate, 1-dodecylazaclo-heptan-2-one , oleic acid, linoleic acid,and mixtures thereof.

11 The method of claim 1, wherein the composition further comprises a cosmetically acceptable vehicle.

12. The method of claim 11, wherein the vehicle is selected from the group consisting of: an emulsion, a gel, and a stick, a suspension, a foam, a stick, a solution, a spray, a patch, a powder and a towelette.

13. The method of claim 1, wherein the composition has a pH less than about 7.5.

14. The method of claim11, wherein the vehicle is anhydrous.

15. The method of claim 1, wherein said topical composition further comprises a secondary component selected from the group consisting of:

a. a rexinoid;
b. an estrogen synthetase (aromatase) stimulating compound;
c. a 5 alpha-reductase activity inhibitor;
d. an exfoliation promoting compound;
e. an ultraviolet (UV) light protecting/sunscreen agent;
f. a barrier function enhancing agent;
g. a barrier function enhancing agent;
h. an elastase inhibitor;
i. a skin lightening agent;
j. an antioxidant;
k. a skin warming agent;
l. a skin cooling compound; and
m. an anti-pruretic/anti-itch compound.

16. The method of claim 15, wherein the secondary component is said sunscreen.

17. The method of claim 16, wherein said sunscreen is selected from the group consisting of:

a. avobenzone;
b. octylmethoxycinnamate;
c. oxybenzone;
d. titanium dioxide;
e. octyl salicylate; and
f. mixtures thereof.

18. A composition for improving the aesthetic appearance of epithelia comprising:

a retinoid in an amount effective to improve the aesthetic appearance of the epithelia; and

a penetration enhancing agent in an amount effective to enhance penetration of said retinoid into the epithelia.

19. The composition of claim 18, further comprising a sunscreen agent selected from the group consisting of :

a. avobenzone;
b. octylmethoxycinnamate;
c. titanium dioxide;
d. octyl salicylate; and
e. mixtures thereof.

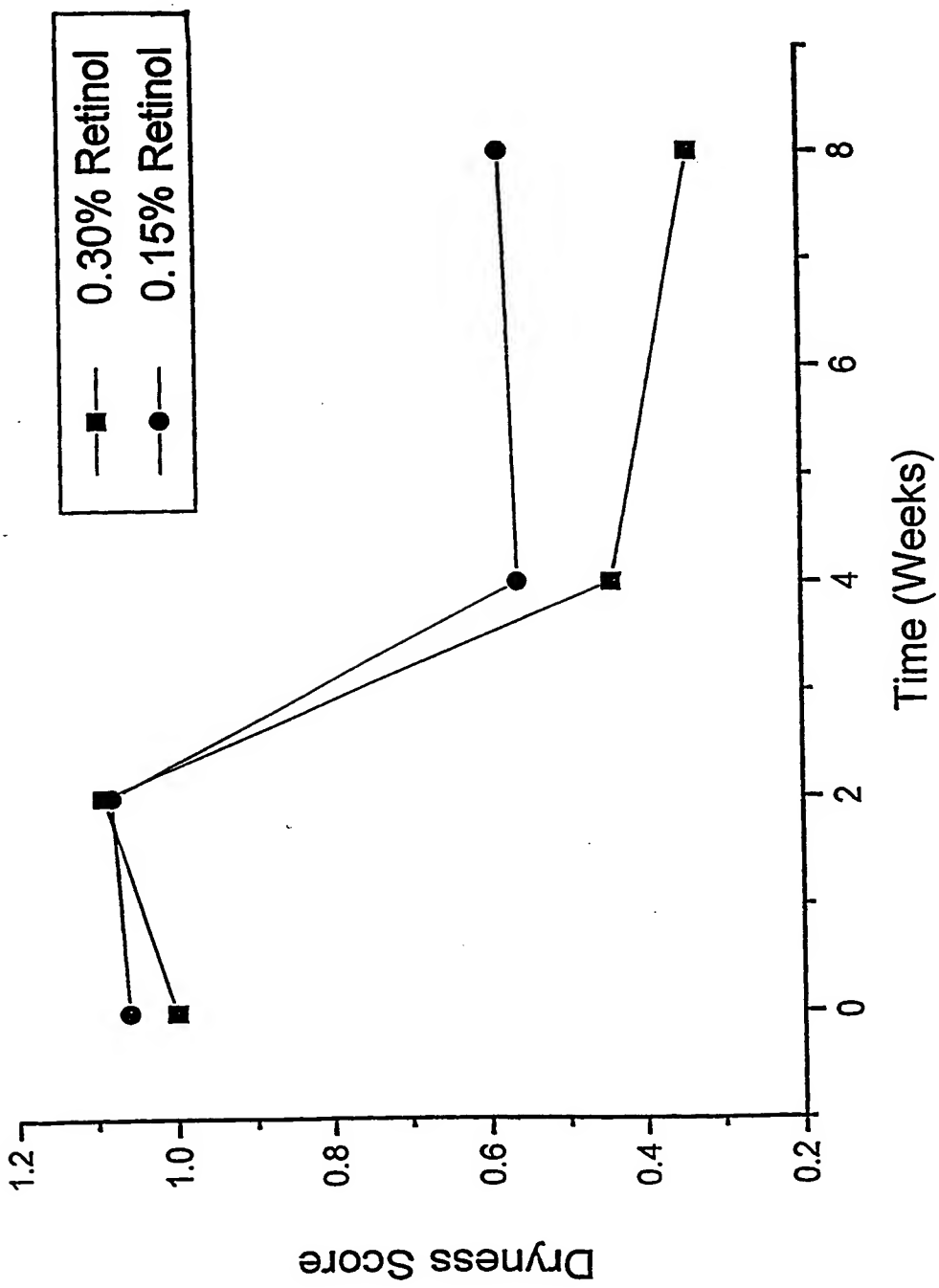

0.30% Retinol
0.15% Retinol
Dryness Score
1.2
1.0
0.8
0.6
0.4
0.2
0
2
4
6
8
Time (Weeks)

Figure 1

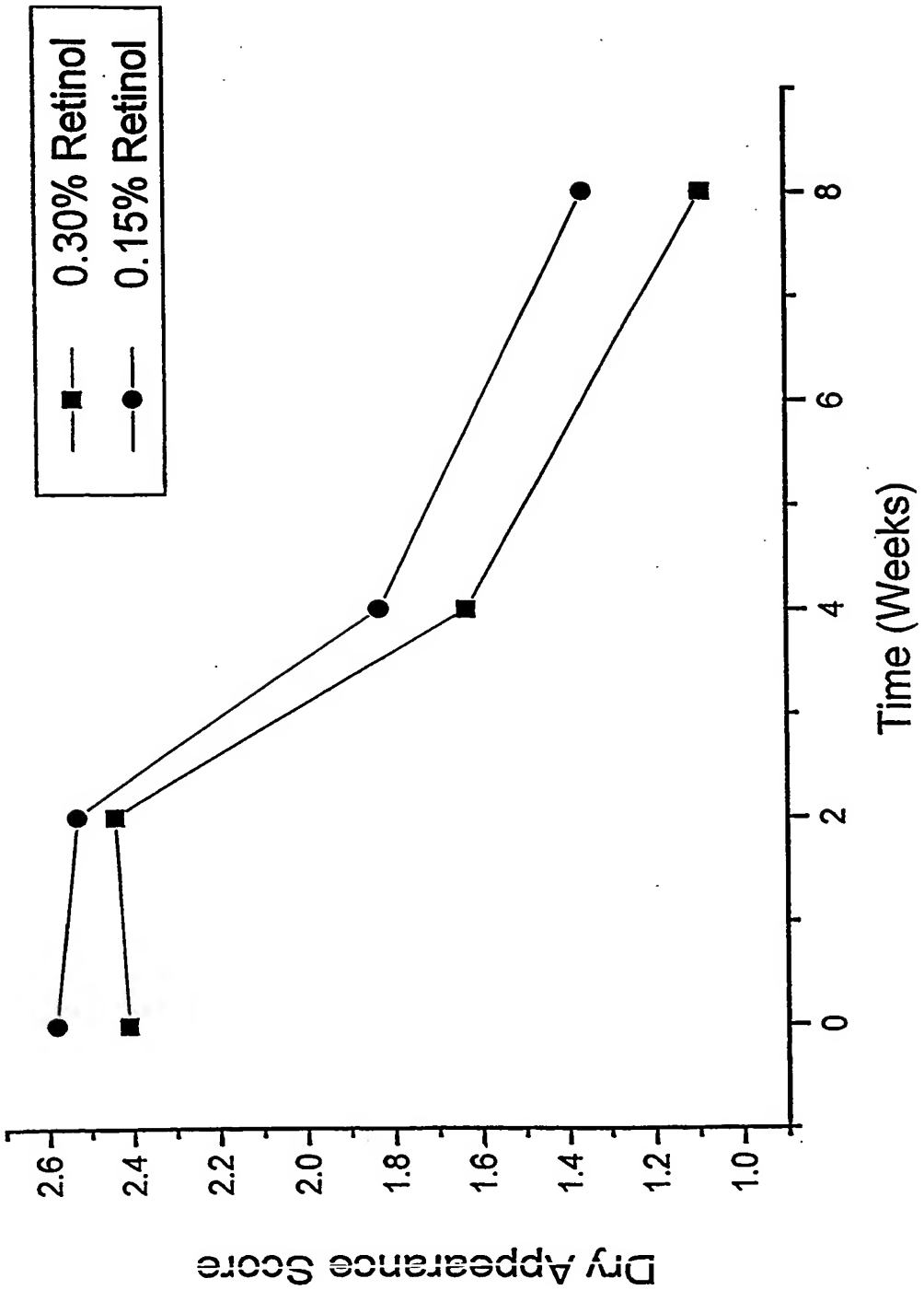
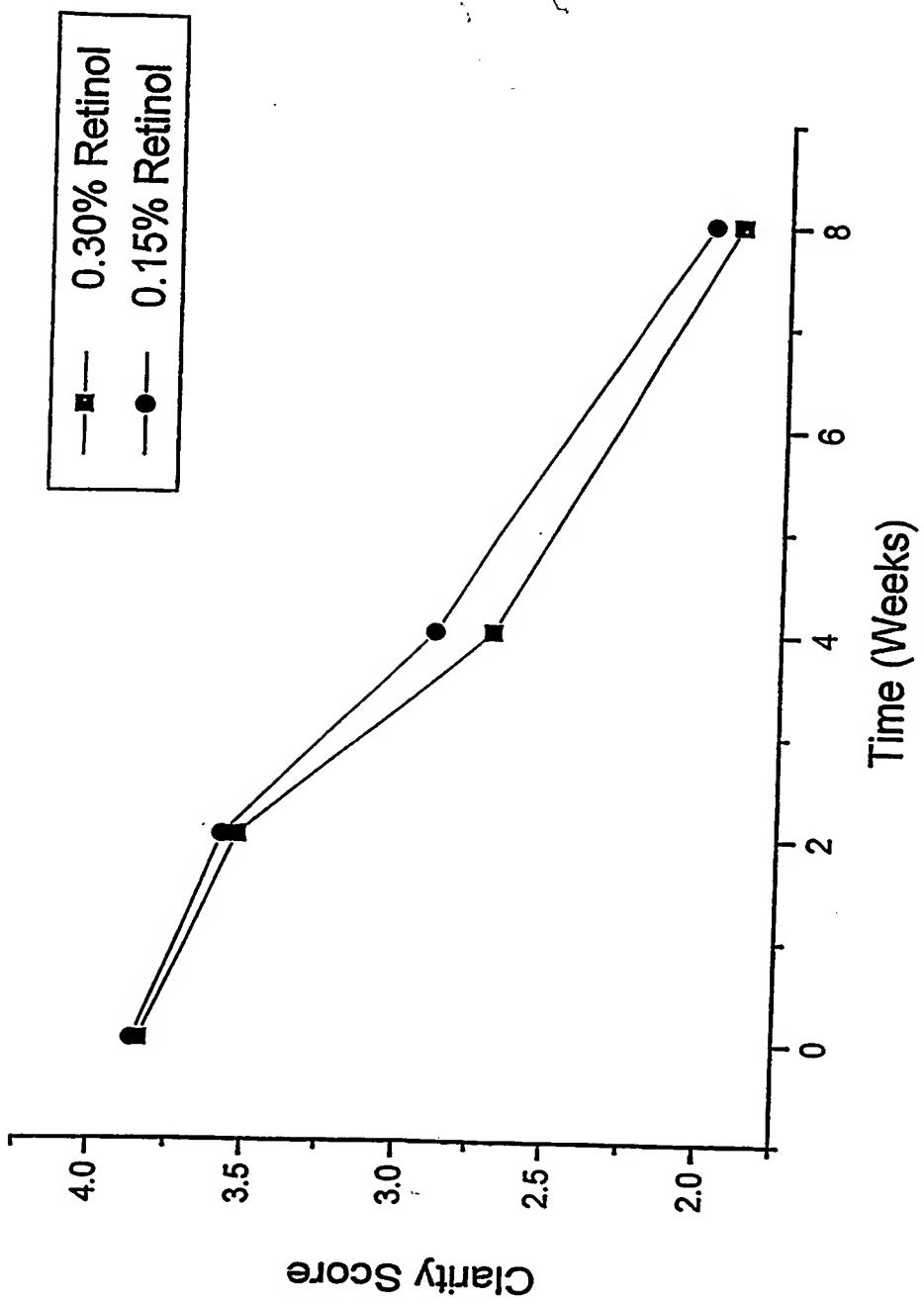

0.30% Retinol
0.15% Retinol
Dry Appearance Score
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0
2
4
6
8
Time (Weeks)

Figure 2


0.30% Retinol
0.15% Retinol
Clarity Score
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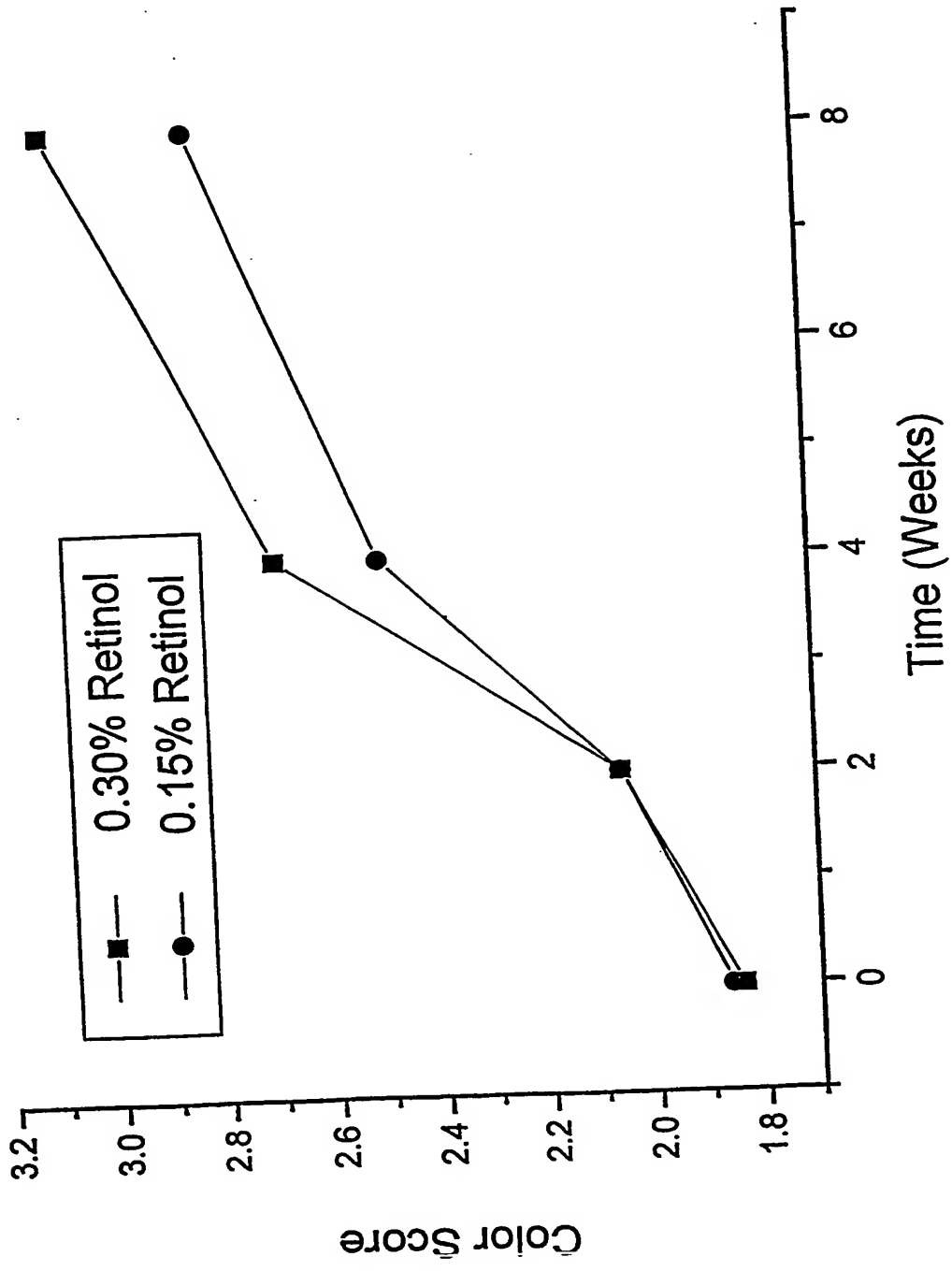
3.0
2.5
2.0
0
2
4
6
8
Time (Weeks)

Figure 3


Color Score
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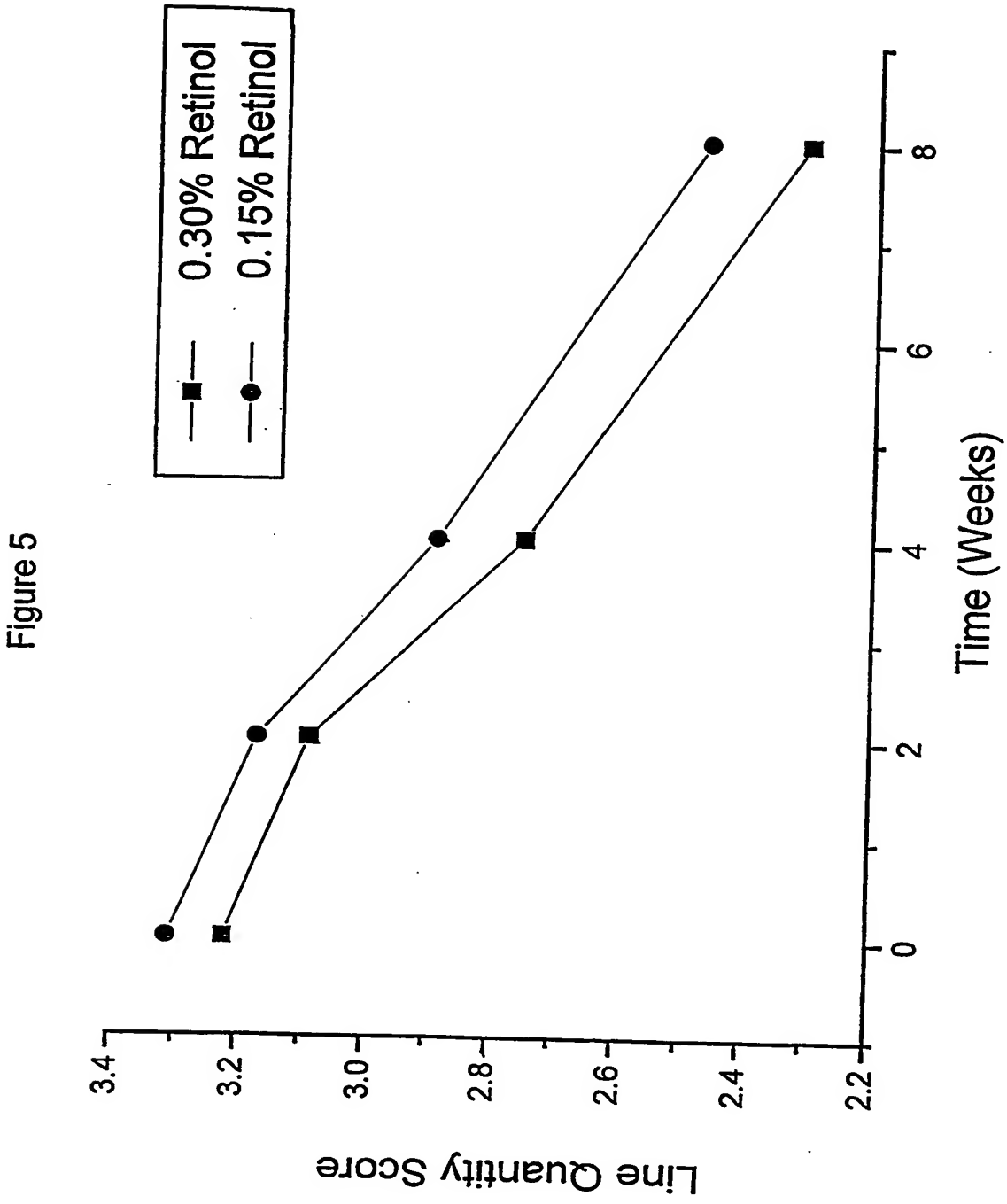
3.0
2.8
2.6
2.4
2.2
2.0
1.8
0
2
4
6
8
Time (Weeks)
0.30% Retinol
0.15% Retinol

Figure 4


0.30% Retinol
0.15% Retinol
Line Quantity Score
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3.0
2.8
2.6
2.4
2.2
0
2
4
6
8
Time (Weeks)

Figure 5

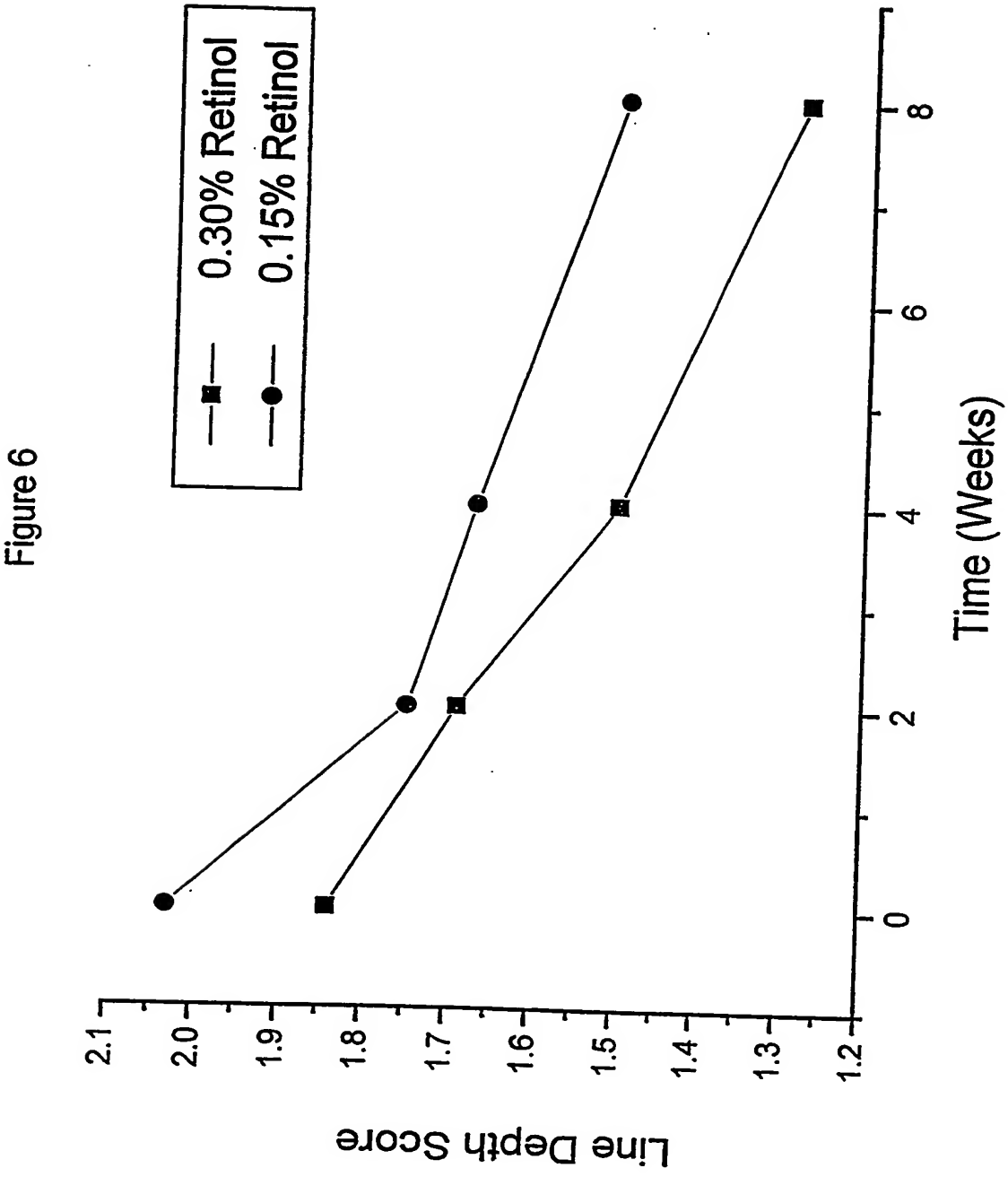
0.30% Retinol
0.15% Retinol
Line Depth Score
2.1
2.0
1.9
1.8
1.7
1.6
1.5
1.4
1.3
1.2
0
2
4
6
8
Time (Weeks)

Figure 6